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(54) PHOSPHATE-BINDING POLYMER PREPARATIONS

(57) Tablets which contain phosphate-binding polymers having an average particle size of 400 µm or less, containing particles of 500 µm or less in particle size at a ratio of at least 90 % and showing a moisture content of 1 to 14 % and crystalline cellulose and/or hydroxypropylcellulose with a low degree of substitution; and a process for producing the same. These tablets have a high active component content and an excellent ability to bind to phosphates and are quickly disintegrated in an acidic to neutral region while being little affected by stirring strength. Thus, they are excellent preparations capable of lessening changes in bioavailability depending on pH value.

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Description

PCT/EP97/00014

TECHNICAL FIELD

[0001] This invention relates to a tablet containing a phosphate-binding polymer, which has an average particle size of 400 μm or less, contains particles of 500 μm or less in particle size at a ratio of 90% or more and has a moisture content of 1 to 14%, together with crystalline cellulose and/or low substituted hydroxypropylcellulose, and showing a rapid disintegration, dispersibility and an ability to bind to phosphate, and a process for producing the same.

10

BACKGROUND ART

RELEVANT Existing Art Disclosure

[0002] Phosphate-binding polymers, which are non-absorptive polymers capable of adsorbing phosphate, are useful as remedies for hyperphosphatemia induced by renal hypofunction such as renal insufficiency. As described in, for example, U.S. Patent No. 5496545, phosphate-binding polymers are publicly known as cationic polymer compounds comprising primary and secondary amines which are prepared by crosslinking polyallylamine with the use of a crosslinking agent such as epichlorohydrin.

[0003] With respect to phosphate-binding polymer preparations as remedies for hyperphosphatemia, for example, U.S. Patent No. 5496545 points out that tablets can be produced by using various additives including crystalline cellulose. However, the patent cited above presents no particular example of such preparations. Although the present inventors attempted in practice to produce tablets by blending various additives with the phosphate-binding polymer obtained by the method as described in the above patent, no tablet could be successfully produced thereby.

[0004] Moreover, known adsorbents for oral administration, for example, a calcium polystyrene sulfonate preparation (KalimateTM, manufactured by Nikken Chemicals Co., Ltd.), a sodium polystyrene sulfonate preparation (KayexalateTM, manufactured by Torii & Co., Ltd.), an adsorptive carbon preparation (KremezinTM manufactured by Kureha Chemical Industry Co., Ltd.), a cholestyramine preparation (QuestranTM, manufactured by Bristol-Myers Squibb Co.) and a precipitated calcium carbonate preparation (manufactured by Emisu Yakuhin K.K.), are all in dosage forms of bulk powders, powder preparations or capsules containing powders. Namely, there has been reported no example of preparations of this type in the form of tablets so far.

[0005] When orally administered, phosphate-binding polymers adsorb phosphorus in foods followed by excretion into the feces to thereby inhibit the absorption of phosphorus via the digestive tracts, thus regulating the phosphorus concentration in the blood. These phosphate-binding polymers are taken in a relatively large single dose, i.e., from 1 to 2 g. Because of reacting with water and thus swelling rapidly, the phosphate-binding polymers can be hardly taken as such.

[0006] Patients with dialysis to whom the phosphate-binding polymers are to be administered as remedies for hyperphosphatemia are frequently under restriction in water intake. It is therefore required to develop phosphate-binding polymer preparations which can be taken with a small amount of water. One of the promising dosage forms is tablets which can be small-sized by compression, in particular, coated tablets which would not disintegrate in the mouth and can be smoothly ingested. When processed into tablets by compressing, however, a phosphate-binding polymer alone gives only a poor tablet hardness, and thus cannot be processed as such into a tablet preparation. Due to the high hygroscopicity and swelling properties of the phosphate-binding polymer, it is also impossible to produce a phosphate-binding polymer preparation by the wet granulation method with the use of water or a binder solution containing alcohols, etc. followed by drying.

[0007] To overcome these problems, it has been required to develop a production process which comprises blending a powdery phosphate-binding polymer with powdery additives having excellent molding characteristics and compressing the obtained mixture. Such a preparation should be designed by taking into consideration changes in the disintegration properties and dispersibility accompanying the compression. Since a phosphate-binding polymer is to be taken in a relatively large single dose, special regard should be paid to give a preparation with a high content of the active component.

[0008] Although the present inventors attempted to produce phosphate-binding polymer preparations in the form of tablets by using various additives described in U.S. Patent No. 5496545, they could not produce any favorable tablets which contain phosphate-binding polymer having a sufficient hardness, a rapid disintegrative dispersibility and an ability to bind to phosphate.

55 DISCLOSURE OF THE INVENTION

[0009] Under these circumstances, the present inventors have conducted intensive studies to solve the above-mentioned problems. As a result, they have successfully found that a phosphate-binding polymer tablet which contains

pentadecyl trimethyl ammonium chloride, methyl cellulose, crystalline cellulose, low substituted hydroxypropylcellulose and/or low substituted hydroxypropylcellulose, and showing a rapid disintegrative dispersibility and an ability to bind to phosphate, and a process for producing the same.

a large amount of the phosphate-binding polymer, has a sufficient hardness and shows rapid disintegrative dispersibility, and an ability to bind to phosphate can be obtained by adding specific additives to a phosphate-binding polymer which has certain characteristics, thus completing the present invention. More particularly speaking, they have found that a tablet, which contains a phosphate-binding polymer having an average particle size of 400 μm or less, preferably 250 μm or less, containing particles of 500 μm or less, preferably 300 μm or less, in size at a ratio of 90% or more and having a moisture content of 1 to 14%, together with crystalline cellulose and/or low substituted hydroxypropylcellulose, has excellent characteristics.

BRIEF DESCRIPTION OF THE DRAWINGS

TEA ONLY OPEN AS

[0010]

Fig. 1 provides a graph which shows a relationship between the moisture content of the phosphate-binding polymer and the tablet hardness in Example 2.

Fig. 2 provides a graph which shows a relationship between the moisture content of the phosphate-binding polymer and the disintegration time of the tablet in Example 2.

Fig. 3 provides a graph which shows a relationship between the moisture content of the phosphate-binding polymer and the tablet hardness in Example 3.

Fig. 4 provides a graph which shows a relationship between the moisture content of the phosphate-binding polymer and the disintegration time of the tablet in Example 3.

Fig. 5 provides a graph which shows the disintegration properties (i.e., a relationship between the strokes of the disintegration tester and the tablet hardness) of the phosphate-binding polymer preparation in Example 4.

Fig. 6 provides a graph which shows the phosphate-binding profile of the phosphate-binding polymer preparation in Example 5.

MODE FOR CARRYING OUT THE INVENTION

[0011] As the phosphate-binding polymer to be employed in the present invention, use can be made of, for example, one prepared by grinding the dry phosphate-binding polymer obtained by the method disclosed in U.S. Patent No. 5496545 so as to give a ground material having an average particle size of 400 μm or less, preferably 250 μm or less, and containing particles of 500 μm or less, preferably 300 μm or less, in size at a ratio of 90% or more, and then further regulating the moisture content thereof to 1 to 14%. Among phosphate-binding polymers, a crosslinked polymer obtained by treating polyallylamine with epichlorohydrin is particularly suitable in the present invention.

[0012] It is not preferable that the average particle size of the phosphate-binding polymer exceeds 400 μm , since a sufficient hardness to give tablets can be hardly achieved in this case. When the moisture content of the phosphate-binding polymer is less than 1%, it is also impossible to obtain a sufficient hardness to give tablets and thus the tablet surface is liable to be abraded. When the moisture content thereof exceeds 14%, on the other hand, a sufficient hardness can be achieved. In this case, however, the resultant tablets undergo plastic deformation, which makes them inadequate as a medicinal preparation. To obtain tablets with improved administration properties, it is necessary to impart such surface strength to the tablets as to give a hardness of 6.KP or more (measured with a tablet hardness tester) and a weight loss of 1% or less in an friability test (100 revolutions). Moreover, the tablets should not undergo plastic deformation. To satisfy these requirements, it is required that the moisture content of the polymer falls within a range of 1 to 14%. The expression "a moisture content of 1 to 14%" as used herein means that after drying at 105°C for 16 hours, the weight is reduced by 1 to 14%. It is preferable that the drying weight loss ranges from 2 to 14%. When the phosphate-binding polymer per se absorbs moisture in the course of grinding to give a moisture content of 1 to 14%, the phosphate-binding polymer may be used in the tablets of the present invention as such without regulating the moisture content any more.

[0013] The phosphate-binding polymer may be ground with an arbitrary apparatus without restriction, so long as a particle size of 500 μm or less and the average particle size as defined above can be achieved thereby. For example, use may be made of an impact grinder therefor.

[0014] The moisture content may be regulated by using a moisture-controlling agent, for example, a saturated aqueous solution of sodium chloride (25°C, relative humidity 75.3%), a saturated aqueous solution of calcium chloride (25°C, relative humidity 84.3%), a saturated aqueous solution of magnesium nitrate (25°C, relative humidity 52.8%), etc. or allowing the polymer to spontaneously absorb the moisture in the atmosphere. It is also possible to prepare the phosphate-binding polymer in such a manner as to give a moisture content within the range of 1 to 14% to thereby provide the polymer with the desired moisture content.

[0015] Although the crystalline cellulose to be used in the present invention is not particularly restricted, use may be made therefor of one showing a weight loss of 7% or less after drying at 105°C for 3 hours. It is preferable to use

marketed products, for example, Avicel™ PH101, PH102, PH301, PH302, etc. (manufactured by Asahi Chemical Industry Co., Ltd.) either alone or as a mixture thereof.

[0016] The low substituted hydroxypropylcellulose to be used in the present invention means one having a degree of substitution by hydroxypropoxy group (-OC₃H₆OH) of 5.0 to 16.0% by weight. As a low substituted hydroxypropylcellulose, it is preferable to use marketed products such as LH-11, LH-21, LH-31, etc. (manufactured by Shin-Etsu Chemical Co., Ltd.) either alone or as a mixture thereof.

[0017] The amounts of the crystalline cellulose and/or the low substituted hydroxypropylcellulose to be used in the phosphate-binding polymer tablet according to the present invention may be arbitrarily determined by taking the dose of the phosphate-binding polymer as an oral preparation and the administration properties of the preparation into consideration. In a preferable embodiment, for example, the crystalline cellulose and/or the low substituted hydroxypropylcellulose are used in an amount of 10% by weight or more, preferably 30% by weight or more, based on the phosphate-binding polymer which has an average particle size of 250 µm or less, contains particles of 300 µm or less in size at a ratio of 90% or more and has a moisture content of 1 to 14%. When both of the crystalline cellulose and the low substituted hydroxypropylcellulose are added, it is preferable that the sum of the contents of these components is 10% by weight or more, preferably 30% by weight or more. From the viewpoint of the administration properties, etc. of the preparation, the upper limit of the content of the crystalline cellulose and/or the low substituted hydroxypropylcellulose is from 50 to 200% by weight.

[0018] Since the phosphate-binding polymer and the crystalline cellulose or the low substituted hydroxypropylcellulose have highly frictional natures, it is recommended to use a hydrogenated oil in the step of the continuous tabletting so as to relieve the load due to the rubbing between the blend and the punch of a tabletting machine. As the hydrogenated oil, use may be made of a marketed product such as Lubriwax™ manufactured by Freund Industrial Co., Ltd..

[0019] The phosphate-binding polymer tablet according to the present invention can be produced by blending the phosphate-binding polymer with the crystalline cellulose and/or low substituted hydroxypropylcellulose together with fillers (lactose, sucrose, mannitol, etc.), lubricants (magnesium stearate, polyethylene glycol, etc.), other additives conventionally employed in the art, perfumes, coloring agents, etc. followed by tabletting.

[0020] The phosphate-binding polymer tablet according to the present invention may be further processed into a film-coated tablet by coating the surface thereof with a film. In the film-coating, use may be made of water-soluble film bases such as hydroxypropylmethylcellulose and acrylic copolymers. It is particularly preferable to use hydroxypropylmethylcellulose therefor.

[0021] To further illustrate the present invention in greater detail, the following Examples and Referential Example will be given. However, it is to be understood that the present invention is not restricted thereto.

Referential Example

[0022] Epichlorohydrin was added as a crosslinking agent to polyallylamine and crosslinking polymerization was carried out to give a cationic phosphate-binding polymer wherein the primary amine (81.2% by mol) and the secondary amine (18.1% by mol) formed hydrochlorides at a ratio of about 40%. The obtained polymer was vacuum-dried to give a dry powder. This dry powder of the phosphate-binding polymer was ground by using a Fitz Mill (Model M5A manufactured by Fitzpatrick) and thus a moisture-containing phosphate-binding polymer (moisture content: 3.6%, ratio of particles of 300 µm or less in size: 99.7%) was obtained.

Example 1

[0023] To 150 mg of the moisture-containing phosphate-binding polymer obtained in the above Referential Example, either crystalline cellulose (Avicel™ PH101 manufactured by Asahi Chemical Industry Co., Ltd.) or low substituted hydroxypropylcellulose (L-HPC LH31 manufactured by Shin-Etsu Chemical Co., Ltd.) was added in an amount of 150 mg, i.e., 100% by weight based on the weight of the phosphate-binding polymer. The obtained mixture was compressed under a static pressure (500 kg, 1,000 kg or 1500 kg) to give a tablet (diameter: 10 mm) weighing 300 mg. For comparison, 150 mg of the moisture-containing phosphate-binding polymer was blended with 150 mg of one additive selected from among lactose (200M DMV), mannitol (manufactured by Kyowa Hakko Kogyo Co., Ltd.), methylcellulose (Metolose™ SM-15 manufactured by Shin-Etsu Chemical Co., Ltd.), talc (manufactured by Kihara Kasei), hydroxypropylcellulose (HPC-L manufactured by Nippon Soda Co., Ltd.), hydroxypropylmethylcellulose 2910 (HPMC-TC-5-RW manufactured by Shin-Etsu Chemical Co., Ltd.) carmellose calcium (ECG-505™ manufactured by Gotoku Yakuhiin). The obtained mixture was compressed under a static pressure (500 kg, 1,000 kg or 1500 kg) to give a tablet (diameter: 10 mm) weighing 300 mg. Further, 300 mg of the moisture-containing phosphate-binding polymer was compressed under a static pressure to give a control tablet.

[0024] The hardness of each tablet thus obtained was measured with a hardness tester (Pharmatest). Also, tablets showing a hardness of 6 KP or more at a compression pressure of 1,000 kg were tested by using a disintegration tester.

(manufactured by Toyama Sangyo) with the use of water as a test fluid. Table 1 summarizes the results.

Table 1

Tablet hardness (KP) (compression pressure: kg)

Additive	Tablet hardness (KP) (compression pressure: kg)	Disintegration 1000 kg (min)
crystalline cellulose (50% based on phosphate-binding polymer)	500	1000
lactose	500	1500
mannitol	9.4	17.7
L-HPC	5.4	24.1
methylcellulose	0.7	0.5
talc	0.4	1.8
ECG-505 (control)	10.2	20.0
HPC-L (control)	13.3	22.6
HPMC	4.8	10.1
ECG-505 (control)	1.3	5.0
(control)	0.5	1.5

[0025] As Table 1 shows, the tablets showing hardness exceeding 6 KP and disintegration time not longer than 15 minutes could be obtained by using crystalline cellulose or low substituted hydroxypropylcellulose (L-HPC).

Example 2

[0026] The moisture-containing phosphate-binding polymer obtained in the above Referential Example was dried at 105°C for 16 hours to give a dry phosphate-binding polymer powder (moisture content: less than 0.1%). In a desiccator, this dry powder was allowed to absorb moisture with the use of a saturated aqueous solution of sodium chloride as a moisture-controlling agent so as to prepare phosphate-binding polymers with moisture contents of 1.1 to 16.4%.

[0027] 200 mg of each of these phosphate-binding polymers differing in moisture content was blended with 100 mg of crystalline cellulose (50% by weight based on the phosphate-binding polymer) and the resultant mixture was compressed under a static pressure of 1,000 kg to give a tablet (diameter: 10 mm) weighing 300 mg.

[0028] For comparison, 300 mg of each these phosphate-binding polymers differing in moisture content was compressed under a static pressure of 1,000 kg to give a tablet (diameter: 10 mm) weighing 300 mg.

[0029] The hardness of each tablet thus obtained was measured with a hardness tester. Fig. 1 shows the results. Moreover, tablets showing hardness of about 6 KP were each subjected to a friability test by revolving 100 times with the use of a friability tester (25 rpm, 4 minutes) and then the weight loss was determined. Table 2 summarizes the results.

Table 2

Tablet composition	Moisture content in phosphate-binding polymer	Tablet hardness (KP)	Friability (wt.loss:%)
phosphate-binding polymer 300 mg	6.1%	8.0	3.6
phosphate-binding polymer 200 mg	1.1%	7.9	0.7
crystalline cellulose 100 mg	< 0.1%	5.3	0.8
phosphate-binding polymer 200 mg	< 0.1%	5.6	1.6
crystalline cellulose 100 mg	< 0.1%	5.6	1.6

[0030] As Figs. 1 and 2, and Table 2 show, the tablet produced by comprising the phosphate-binding polymer alone

could not achieve sufficient hardness (6 KP or more) at a moisture content of 5% or less. Although the tablet with a moisture content of 6.1% showed a hardness of 8 KP, the friability exceeded the allowable level (weight loss: 1% or less) specified in United States Pharmacopoeia. That is to say, it had a poor surface strength. In the tablets produced by compressing the phosphate-binding polymer containing 9% or more moisture alone, the disintegration time was prolonged with an increase in the tablet hardness. The tablets with moisture content of 16% or more suffered from plastic deformation, thus showing inadequate tablet properties. When the phosphate-binding polymer was blended with crystalline cellulose, in contrast thereto, a sufficient hardness and tablet surface strength were observed and rapid disintegration (disintegration time: about 1 minute) was achieved within a moisture content range of 1 to 14%.

Example 3

[0031] The moisture-containing phosphate-binding polymer obtained in the above Referential Example was sieved by using a sonic shifter (manufactured by Seishin Kogyo) through 60 mesh (250 µm), 80 mesh (180 µm), 150 mesh (106 µm) and 270 mesh (53 µm) sieves to give a phosphate-binding polymer of 250 µm or more in average particle size, one of from 180 to 250 µm in average particle size, one of from 106 to 180 µm in average particle size, one of from 53 to 106 µm in average particle size and one of 53 µm or less in average particle size.

[0032] To 200 mg of each of these phosphate-binding polymers differing in average particle size, 100 mg of crystalline cellulose (50% by weight based on the weight of the phosphate-binding polymer) was added and the obtained mixture was compressed under a static pressure of 1,000 kg to give a tablet (diameter: 10 mm) weighing 300 mg.

[0033] For comparison, 300 mg of each of the phosphate-binding polymers differing in average particle size was compressed alone under a static pressure of 1,000 kg to give a tablet (diameter: 10 mm) weighing 300 mg.

[0034] Fig. 3 shows the results of the measurement of the hardness of each tablet thus obtained with a hardness tester, while Fig. 4 shows the results of the determination of the disintegration time thereof (test fluid: water).

[0035] As Figs. 3 and 4 show, none of the tablets produced by compressing the phosphate-binding polymers alone could achieve a sufficient hardness (6 KP or more). When crystalline cellulose was added to the phosphate-binding polymers, in contrast thereto, the hardness was elevated with a decrease in the average particle size. A sufficient hardness and rapid disintegration were established at an average particle size of 250 µm or less.

Example 4

[0036] 200 g of the moisture-containing phosphate-binding polymer obtained in the above Referential Example was blended with 97.6 g of crystalline cellulose and 2.4 g of magnesium stearate (manufactured by Nitto Kasei) employed as a lubricant. The obtained mixture was compressed by using a rotary tabletting machine (Model HT-P18A manufactured by Hata Iron Worker) under a pressure of 2,000 kg to give tablets (uncoated) of 9.5 mm in diameter each weighing 300 mg and containing 200 mg of the phosphate-binding polymer.

[0037] When measured with a hardness tester (a confeter), these tablets showed a tablet hardness of 7.7 KP.

[0038] Further, the uncoated tablet containing 200 mg of the phosphate-binding polymer was coated with a film comprising 8.25 mg of hydroxypropylmethylcellulose 2910 (HPMC-TC-5-MW manufactured by Shin-Etsu Chemical Co., Ltd.), 1.26 mg of polyethylene glycol 6000 (manufactured by Nippon Oil and Fats Co., Ltd.), 1.8 mg of titanium oxide (A-100 manufactured by Ishihara Sangyo Co., Ltd.) and 0.69 mg of talc by using a coating machine (Dria Coater Model DRC-500 manufactured by Powrex Corporation) to give a film-coated tablet preparation.

[0039] The film-coated tablets thus obtained were tested by using a disintegration tester at 5 to 30 strokes per minute with the use of two test fluids (pH 1.2: official liquid 1; specified in Japanese Pharmacopoeia; water). Fig. 5 shows the results.

[0040] As Fig. 5 shows, the phosphate-binding polymer preparation containing crystalline cellulose was rapidly disintegrated within the acidic to neutral region while scarcely affected by the stirring strength (stroke).

Example 5

[0041] To evaluate the drug effects, 5 uncoated tablets and 5 film-coated tablets, each containing 200 mg of the phosphate-binding polymer, prepared in Example 4 were examined in the ability to bind to phosphate in 200 ml of a test fluid which had been prepared by dissolving 4.7 g of sodium chloride, 21.3 g of N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid and 0.544 g of potassium dihydrogenphosphate in water, regulating the pH value to 7 and heating to 37°C, while rotating puddles at 100 rpm. The ability to bind to phosphate was evaluated by monitoring the residual phosphate concentration in the test fluid with the passage of time throughout the process of the disintegration of the tablets, dispersion of the phosphate-binding polymer and adsorption of phosphate. The initial phosphate concentration in the test fluid and the one at the completion of the adsorption are referred to respectively as 1 and 0. Fig. 6 shows the results. The initial phosphate concentration is given by the following formula: $A = \frac{C_0 - C}{C_0} \times 100$, where C_0 is the initial phosphate concentration in the test fluid and C is the phosphate concentration at the completion of the adsorption.

[0042] As Fig. 6 shows, the phosphate-binding polymer preparations containing crystalline-cellulose were able to rapidly bind to phosphate.

INDUSTRIAL APPLICABILITY

[0043] The phosphate-binding-polymer tablet according to the present invention contains the active component at a high ratio, has excellent ability to bind to phosphate and undergoes rapid disintegration within an acidic to neutral region while scarcely affected by the stirring strength. Accordingly, it is an excellent preparation capable of regulating charges in bioavailability due to the gastrointestinal motions and pH value.

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Claims

1. A tablet containing a phosphate-binding polymer, which has an average particle size of 400 μm or less, contains particles of 500 μm or less in size at a ratio of 90% or more and has a moisture content of 1 to 14%, together with crystalline cellulose and/or low substituted hydroxypropylcellulose.
2. The tablet as claimed in claim 1, wherein said phosphate-binding polymer has an average particle size of 250 μm or less and contains particles of 300 μm or less in size at a ratio of 90% or more.
3. The tablet as claimed in claim 1 or 2, wherein the content of crystalline cellulose and/or low substituted hydroxypropylcellulose is 10% by weight or more based on the weight of said phosphate-binding polymer.
4. The tablet as claimed in claim 1, 2 or 3, wherein said low substituted hydroxypropylcellulose has a degree of hydroxypropoxyl-substitution of from 5.0 to 16.0% by weight.
5. The tablet as claimed in any of claims 1 to 4, wherein said phosphate-binding polymer is a polymer disclosed in U.S. Patent No. 5496545, namely

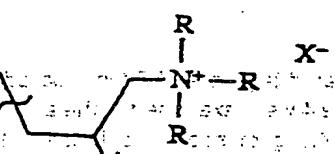
(a) a polymer characterized by a repeating unit having the formula $\text{CH}_2-\text{C}(\text{R})=\text{C}(\text{R})-\text{CH}_2$ where R is a substituent; **(b)** a polymer characterized by a repeating unit having the formula $\text{CH}_2-\text{C}(\text{R})=\text{C}(\text{R})-\text{CH}_2$ where R is a substituent;

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It is also believed that the **R005** and **R006** clusters are located near the **R003** cluster.

or a copolymer thereof, wherein n is an integer and each R_i independently, is H or a loweralkyl (e.g., having between 1 and 5 carbon atoms, inclusive); alkylamino (e.g., having between 1 and 5 carbon atoms, inclusive); or aryl (e.g., phenyl) group;

(b) a polymer characterized by a repeating unit having the formula

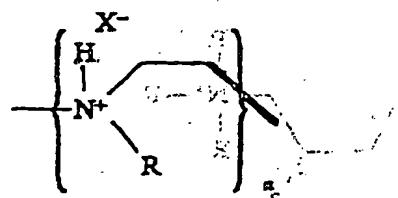


wherein each R_n is selected from the group consisting of H, alkyl (e.g., having between 1 and 5 carbon atoms, inclusive), alkenyl (e.g., having between 2 and 5 carbon atoms, inclusive), alkylamino (e.g., having between 1 and 5 carbon atoms, inclusive), and aryl (e.g., phenyl) groups; and X⁻ is an exchangeable negatively charged counterion selected from the group consisting of organic ions, inorganic ions or combinations thereof;

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wherein each R, independently, is H or a lower alkyl (e.g., having between 1 and 5 carbon atoms, inclusive), alkylamino (e.g., having between 1 and 5 carbon atoms, inclusive), or aryl group (e.g., phenyl);

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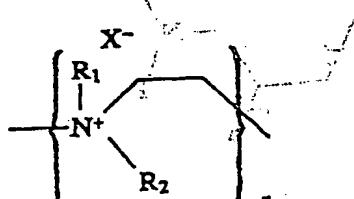
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wherein each n, independently, is an integer, and R is H or a lower alkyl (e.g., having between 1 and 5 carbon atoms, inclusive), alkylamino (e.g., having between 1 and 5 carbon atoms, inclusive), or aryl group (e.g., phenyl);

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(f) a polymer characterized by a repeating unit having the formula

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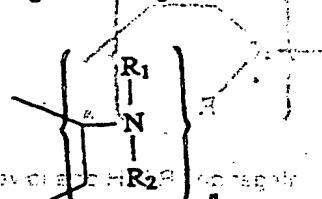
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or a copolymer thereof, wherein n is an integer, and each R₁ or R₂, independently, is H or a lower alkyl (e.g., having between 1 and 5 carbon atoms, inclusive), alkylamino (e.g., having between 1 and 5 carbon atoms, inclusive), or aryl group (e.g., phenyl), and each X is an exchangeable negatively charged counterion selected from the group consisting of organic ions, inorganic ions or combinations thereof;

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(g) a polymer characterized by a repeating unit having the formula

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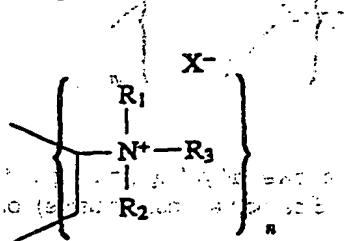
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or a copolymer thereof, wherein n is an integer, each R₁ or R₂, independently, is H, an alkyl group containing 1 to 20 carbon atoms, an alkylamino group (e.g., having between 1 and 5 carbon atoms, inclusive), or an aryl group containing 1 to 12 atoms (e.g., phenyl);

45

(h) a polymer characterized by a repeating unit having the formula

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or a copolymer thereof, wherein n is an integer and each R₁, R₂ and R₃, independently, is H, an alkyl group containing 1 to 20 carbon atoms, an alkylamino group (e.g., having between 1 and 5 carbon atoms, inclusive) or an aryl group containing 1 to 12 atoms (e.g., phenyl), and each X is an exchangeable negatively charged

counterion selected from the group consisting of organic ions, inorganic ions or combinations thereof.

6. The tablet as claimed in any of claims 1 to 5, wherein said phosphate-binding polymer is a polymer obtained by treating polyallylamine with epichlorohydrin so as to crosslink the same.
7. The tablet as claimed in any of claims 1 to 6, which further contains a hydrogenated oil.
8. The tablet as claimed in any of claims 1 to 7, which is further surface-coated with a water-soluble film base.
9. A process for producing phosphate-binding polymer tablet which comprises grinding polyallylamine or a phosphate-binding polymer obtained by crosslinking the same so as to give a ground material having an average particle size of 400 µm or less and containing particles of 500 µm or less in size at a ratio of 90% or more, regulating the moisture content thereof to 1 to 14%, blending the ground material with crystalline cellulose and/or low substituted hydroxypropylcellulose, and then tabletting the resultant mixture.
10. The process as claimed in claim 9, wherein said phosphate-binding polymer is ground so as to give ground material having an average particle size of 250 µm or less and containing particles of 300 µm or less in size at a ratio of 90% or more.
11. Use of a phosphate-binding polymer, which has an average particle size of 400 µm or less, contains particles of 500 µm or less in size at a ratio of 90 % or more and has a moisture content of 1 to 14 %, together with crystalline cellulose and/or low substituted hydroxypropylcellulose for the preparation of a tablet for the treatment of hyperphosphatemia.

100% of patients with symptoms of depression and anxiety.

19.000 रुपये का बिल जो आपको देना चाहिए।

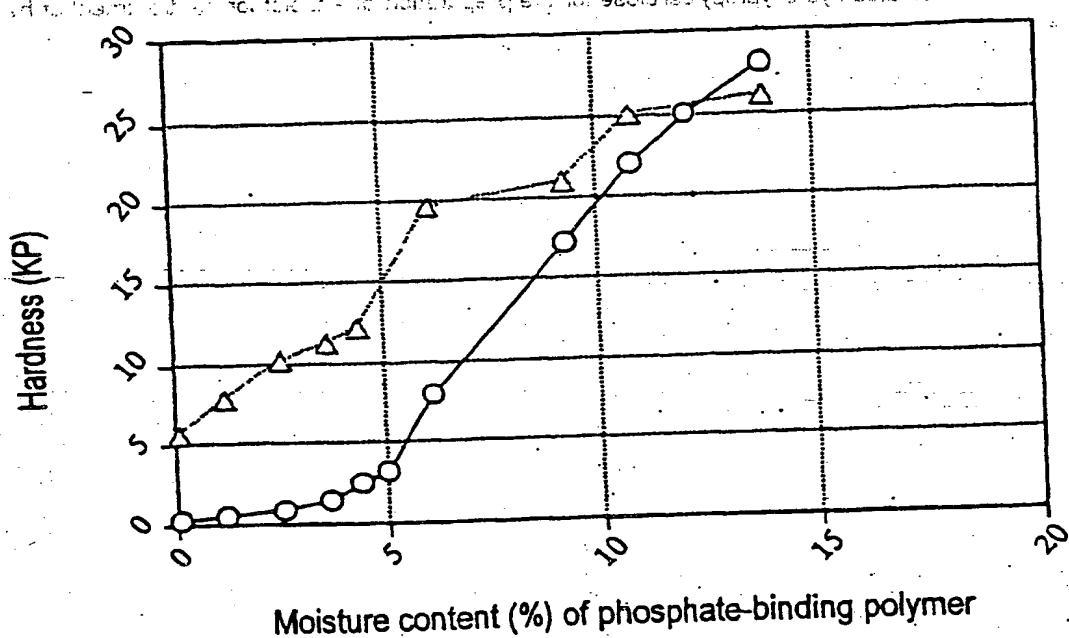
During each of the four days of the study, participants were asked to provide a brief description of their activities and interactions with other people.

Jic de morgan, ja es l'únic resultat que no s'ha oblidat que el teorema de la taula d'

and the U.S. military's capturing additional infiltrators in Iraq, it is clear that the U.S. has not been able to stop the flow of weapons and fighters from Iran to Iraq.

En el momento que se establezca la sanción de la norma, se establecerán procedimientos para su aplicación.

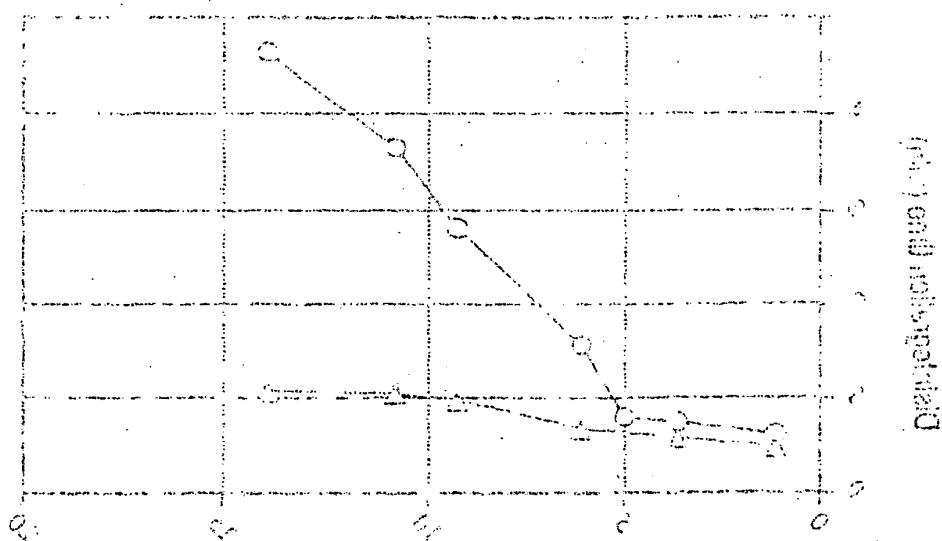
Relationship between moisture content of phosphate-binding polymer and tablet hardness



- 300 mg of phosphate-binding polymer
- △— 200 mg of phosphate-binding polymer + 100 mg of crystalline cellulose

S. S. T.

W. C. (Walter) St. George Johnson, son of Mr. & Mrs. W. C. Johnson,
and his wife, Mrs. L. G. Johnson.

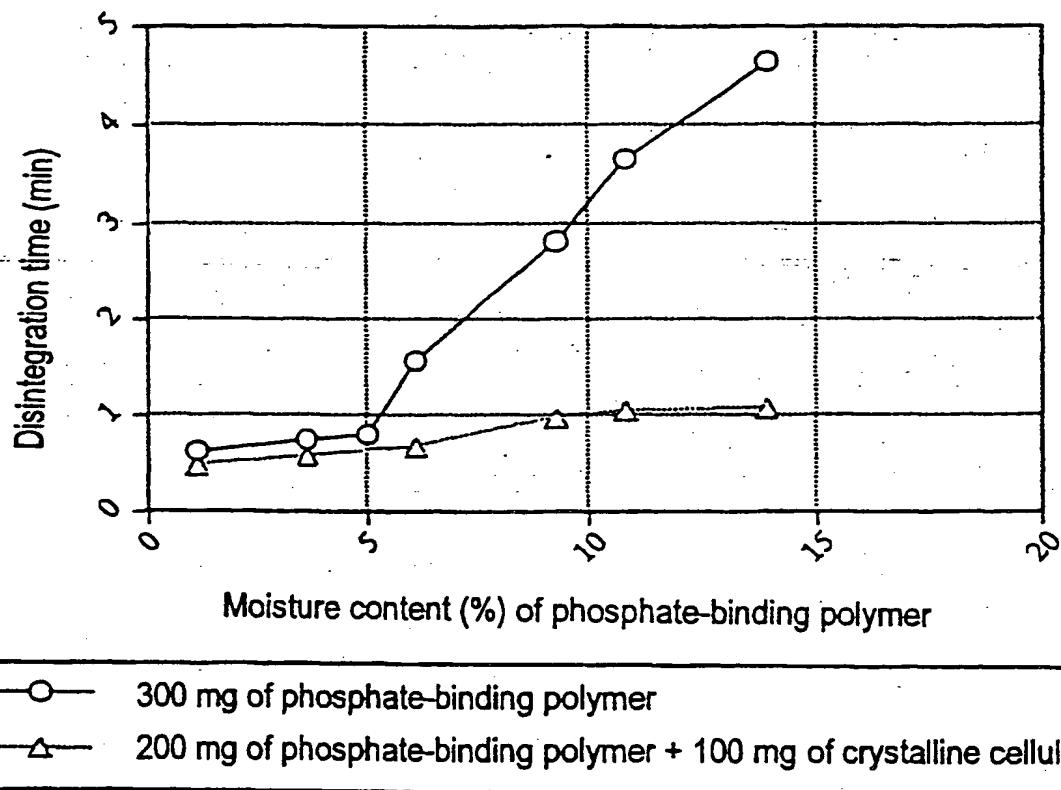


Reaction mixture = aqueous H₂O + starch solution

Reaction mixture = H₂O + starch solution
Reaction mixture = H₂O + starch solution + HCl

Fig. 2

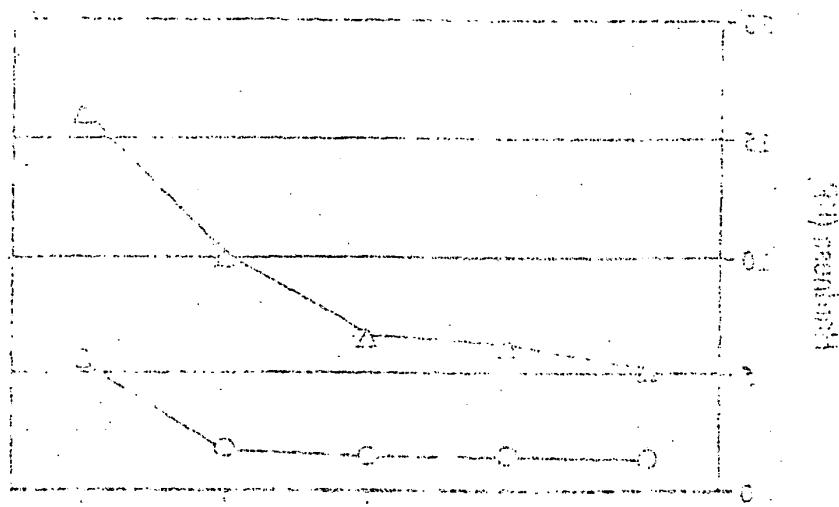
Relationship between moisture content of phosphate-binding polymer and disintegration time



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三

After this I was forced to end class and go home because I had to take care of my mother.



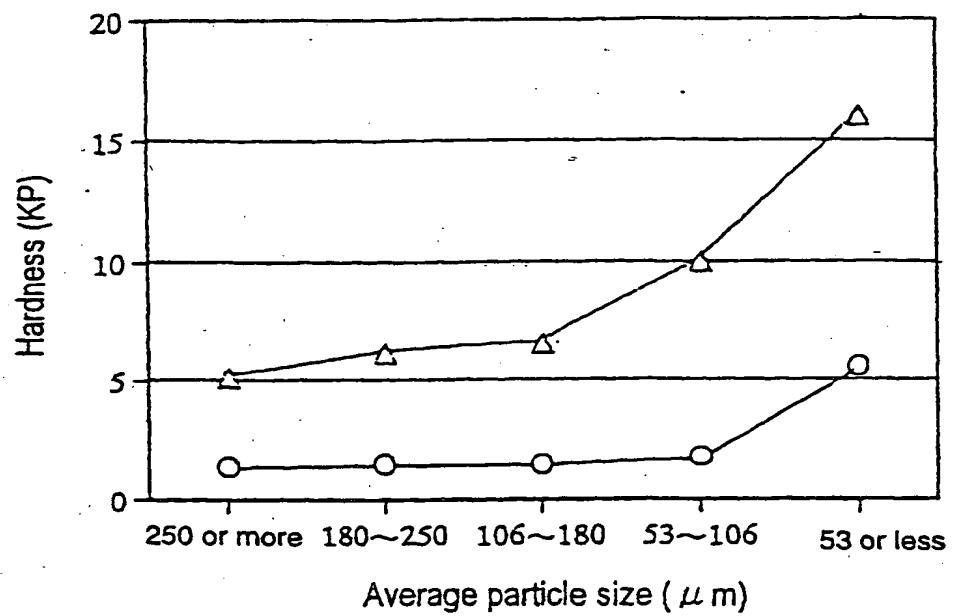
225110 SP 051-30 081-5.1 427-021 442710 C79

(iii) esla esla esla esla

ପ୍ରାଚୀନ କୁଣ୍ଡଳ-ଜାତୀୟ ଲାଭୀ, ୧୦ ମୀ. ୩୦ ।— ୩—
ଏହାରେ ବିଭିନ୍ନ ଶତାବ୍ଦୀ ପରିବର୍ତ୍ତନ ହେଲାମାତ୍ରାମାତ୍ରା ଏହାରେ ବିଭିନ୍ନ

Fig. 3.

Relationship between average particle size of phosphate-binding polymer and tablet hardness



- 300 mg of phosphate-binding polymer
- △— 200 mg of phosphate-binding polymer + 100 mg of crystalline cellulose

b. (2)

1. (b) (5) (A) According to the following figure, respond to the following
point and question. (b) (2)

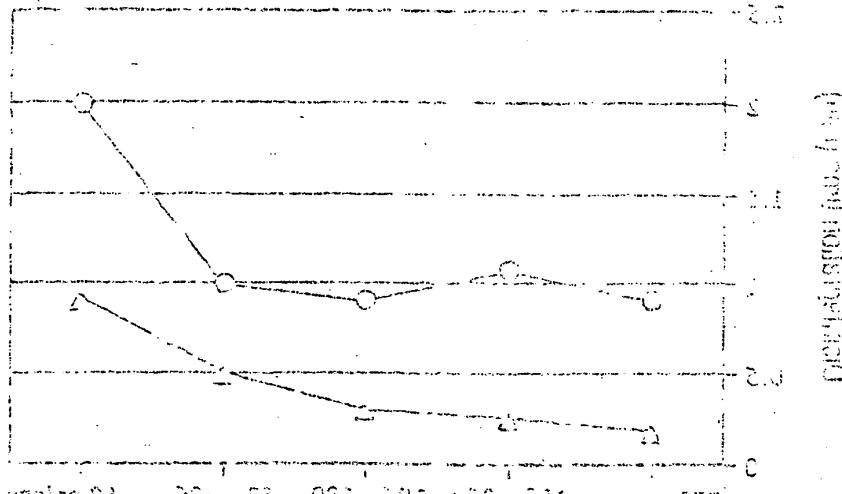
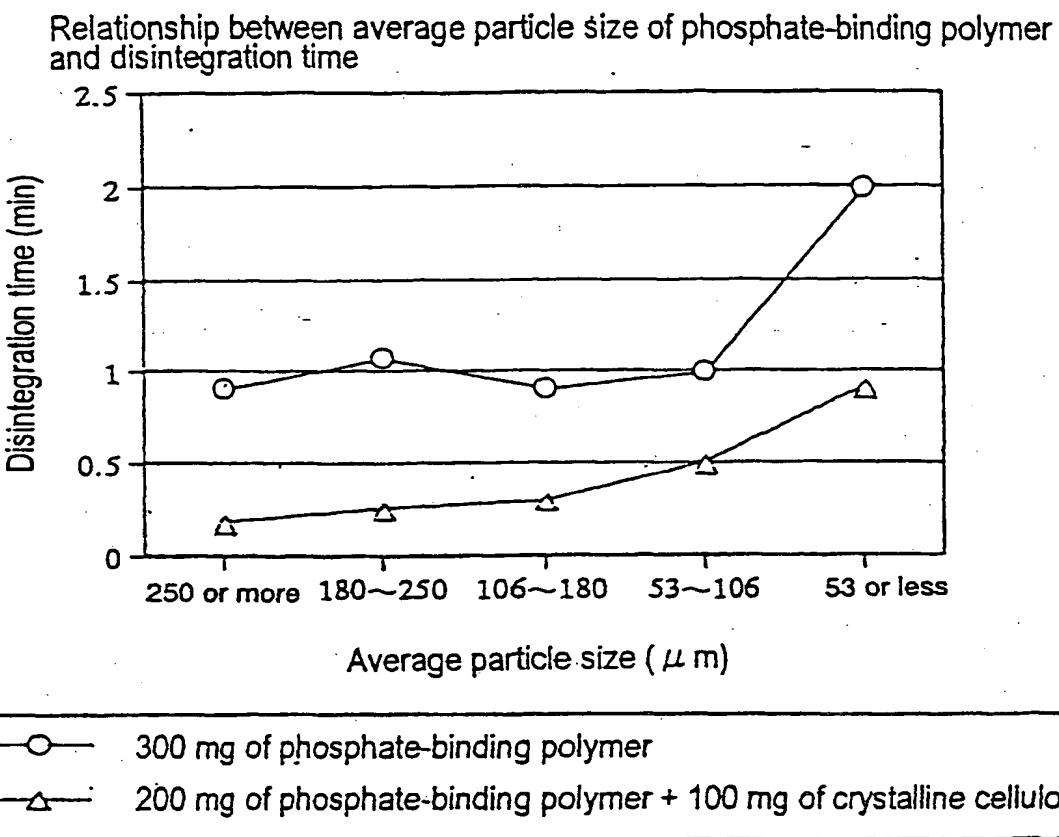


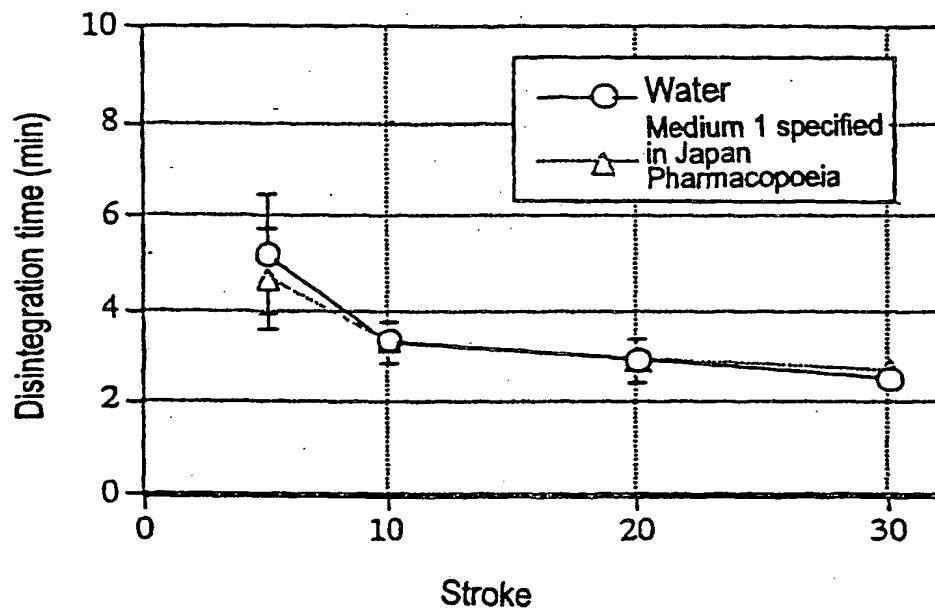
Fig. 4



Days after start of experiment	Dry weight (g) - seedlings + multi-cell	Dry weight (g) - seedlings in slacked peat
0	0.0	0.0
10	~1.5	~1.0
20	~3.0	~2.0
30	~5.5	~3.5

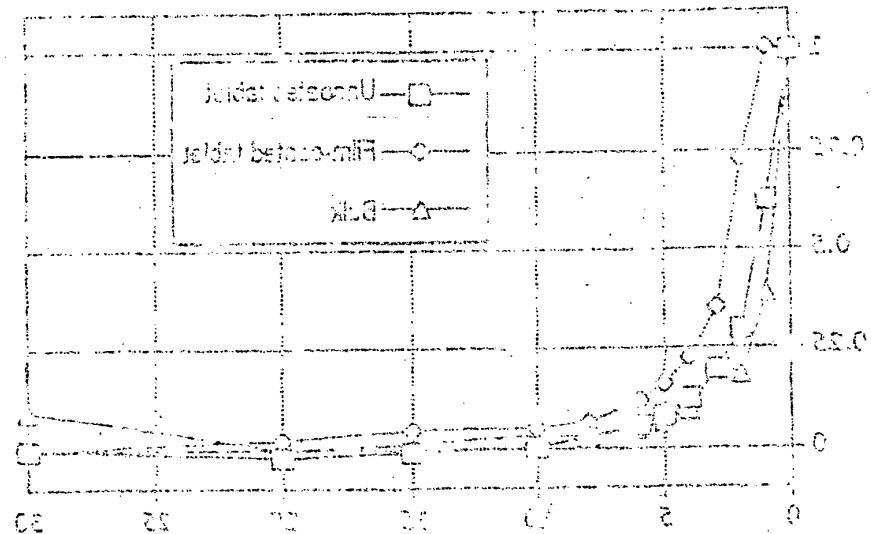
Fig. 5

Disintegration properties of phosphate-binding polymer preparation
Relationship between frequency of stroke and disintegration time



G-10

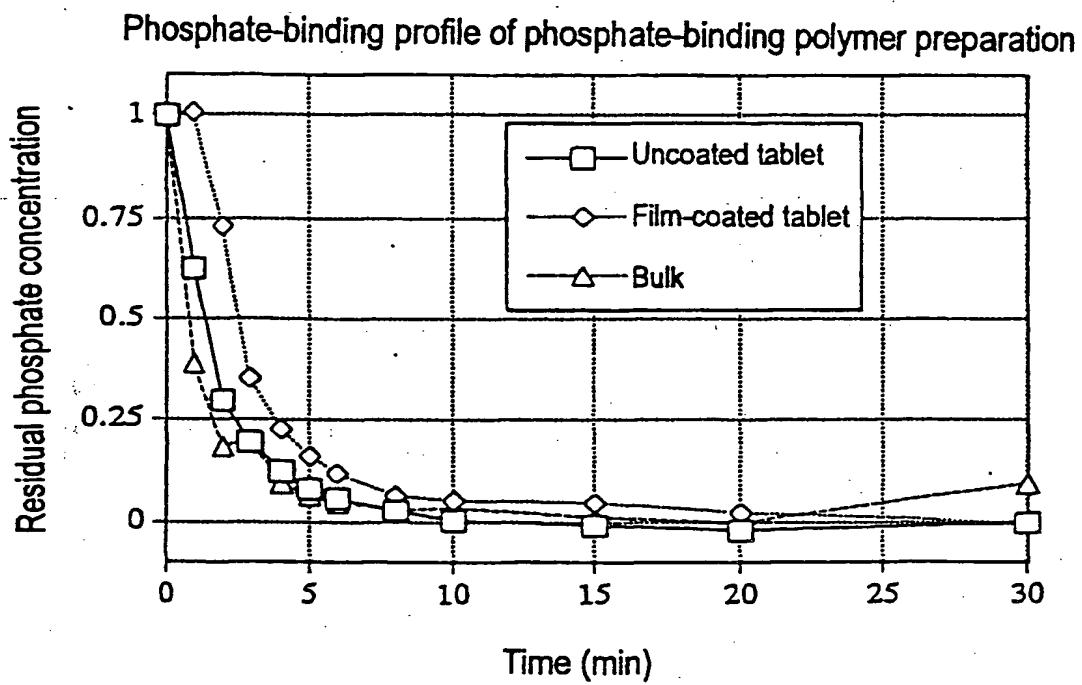
plus equalizing pinhole according to shown scale (feet/degree)



Indicates width of lens

(in) mm.

Fig. 6



RA 8911580

10. PRACTICAL INFORMATION

DEPARTMENT OF THE NAVY - MARINE CORPS
SERIAL 1000, 1870-1918, 10,500

¹ See also the discussion of the relationship between the two types of models in the section on "Theoretical Models."

2000-01-01 10:00:00 2000-01-01 10:00:00 2000-01-01 10:00:00 2000-01-01 10:00:00

VI. What is the specific law to have self-made land? Is the ownership
of land a right or a privilege? Explain. Show that it is a right to own
and cultivate your own land. Give reasons. Do you think
of yourself as a self-sufficient countryman? Do you think that
there is no need for you to buy what you want? If so, why?
If not, why not? Explain.

the reconstruction of society and economy
is a difficult and delicate task, involving the destruction of
old forms of production and distribution, and
the creation of new ones. It is a process that
cannot be completed in a single year, or even two
or three. It must be a long-term endeavour,
based on a clear understanding of the
problems involved and a commitment to
the principles of democracy, justice, equality
and freedom. The reconstruction of society
is a complex and challenging task, but it is
one that must be undertaken if we are to
create a better future for all.

18- .99 .88) 1 51 1 4 88.

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19. Please indicate which one(s) of the following statements best describes your family's financial situation:

1960 MILITARY POLICY AND THE UNITED STATES

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01536

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl' A61K31/785, 9/20, 47/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl' A61K31/785, 9/20, 47/38

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY (STN), CAPLUS (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.:
A	US, 5 496545, A (GelTex Pharmaceuticals Inc.), March 5, 1996 (05. 03. 96) & EP, 716606, A & JP, 9-514782, A	1-10
A	US, 4 631305, A (The Upjohn Company), November 23, 1986 (23. 11. 86) (Family: none)	1-10
A	JP, 5-246861, A (Hokuriku Seiyaku Co., Ltd.), September 24, 1993 (24. 09. 93) & EP, 488139, A & US, 5213806, A	1-10
A	JP, 4-13627, A (Mitsubishi Kasei Corp.), January 17, 1992 (17. 01. 92) (Family: none)	1-10
A	JP, 2-286621, A (Mitsubishi Kasei Corp.), November 26, 1990 (26. 11. 90) (Family: none)	1-10
A	JP, 8-198761, A (Hokuriku Seiyaku Co., Ltd.), August 6, 1996 (06. 08. 96) (Family: none)	1-10

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	
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"E"	earlier document but published on or after the international filing date
"L"	document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"d"	document member of the same patent family

Date of the actual completion of the international search June 10, 1998 (10. 06. 98)	Date of mailing of the international search report June 23, 1998 (23. 06. 98)
Name and mailing address of the ISA/ Japan se Patent Office	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP98/01536

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, 97-04789, A (Hisamitsu Pharmaceutical Co., Inc.), February 13, 1997 (13. 02. 97) & JP, 9-202732, A	1-10
A	JP, 6-157325, A (Mitsubishi Kasei Corp.), June 3, 1994 (03. 06. 94) (Family: none)	1-10
A	JP, 63-253027, A (American Cyanamid Co.), October 20, 1988 (20. 10. 88) & EP, 273209, A & SU, 5215754, A	1-10

Form PCT/ISA/210 (continuation of second sheet) (July 1992)